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(54) Title: TREATMENT OF CANCERS HAVING RESISTANCE TO CHEMOTHERAPEUTIC AGENTS

(57) Abstract: The present invention provides compositions and methods for treating cancer with sorafenib, wherein the cancer that has acquired resistance to another therapeutic agent, such as kinase inhibitors. Sorafinb can also be used to treat cancers which have become refractory to other chemotherapeutic agents .

TREATMENT OF CANCERS HAVING RESISTANCE TO CHEMOTHERAPEUTIC AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of earlier-filed U.S. Provisional Application Ser. Nos. 60/735,853, filed November 14, 2005 and 60/785,347, filed March 24, 2005 which are incorporated herein by reference in its entirety.

DESCRIPTION OF THE INVENTION

[0002] Cancer is a class of diseases characterized by two heritable properties: (1) uncontrolled cell division and (2) the ability of these cells to invade other tissues, either by direct growth into adjacent tissue (invasion) or by migration of cells to distant sites (metastasis). The hyper-proliferative properties initially give rise to a tumor or neoplasm. A tumor is considered a cancer when its cells acquire the ability to invade surrounding tissues, e.g., by breaking loose and entering the blood or lymph systems, or by forming secondary tumors at other sites in the body. The unregulated growth is caused by damaged DNA, resulting in mutations to vital genes that control cell division, the cell cycle, among other functions. One or more of these mutations, which can be inherited or acquired, can lead to uncontrolled cell division and cancer.

[0003] Cancers can be classified according to the tissue and cell type from which they arise. Cancers developing from epithelial cells are called carcinomas, and those from connective and muscle cells are called sarcomas. Additional cancers include those arising from hematopoietic cells (e.g., leukemia) and cancers of the nervous system.

[0004] In general, cancers appear to arise during a process in which an initial population of abnormal cells evolve into more aberrant cells through successive cycles of mutation and selection. More than 100 different genes have been identified which, when mutant, result in cancer. These so-called cancer-critical genes fall into two broad classes: oncogenes and tumor suppressor genes. Many cancer-critical genes play a role in the regulation of cell divisions, a highly complicated process involving multiple and parallel pathways. These include growth factors, cytokines, hormones, etc.

[0005] Cancer can cause many different symptoms, depending on the site and character of the malignancy and whether there is metastasis. A definitive diagnosis usually requires the microscopic examination of tissue obtained by biopsy. Once diagnosed, cancer is usually treated with surgery, chemotherapy and/or radiation.

[0006] If untreated, most cancers eventually cause death. Cancer is one of the leading causes of death in developed countries. It is estimated by the National Cancer Institute that approximately 9.8 million Americans were alive in January 2001 with a history of cancer. About 1,372,910 new cases of cancer were expected to be diagnosed in 2005, alone. In 2005, almost 600,000 Americans died of cancer, about 1 out of every 4 deaths. Many forms of cancer are associated with environmental factors, which may be avoidable. Smoking tobacco leads to more cancers than any other environmental factor.

[0007] Kinase inhibitors are being used successfully to treat cancers; however, some patients acquire a resistance to the drug's activity. In one embodiment, the present invention provides methods of treating a cancer in a subject in need thereof, comprising administering an effective amount of sorafenib to a subject having a cancer, wherein said cancer has acquired resistance to a kinase inhibitor. A kinase inhibitor is any drug or agent (e.g., anti-sense; small molecules; antibodies; etc) which blocks or reduces the activity of a kinase. This includes, tyrosine kinases, serine-threonine kinases, receptor kinases, non-receptor kinases, etc. Generally, a "kinase activity" refers to the ability of a polypeptide to catalyze the transfer of a phosphate from one molecule to another.

[0008] There are a number of well-documented instances where cancers have acquired resistance to a kinase inhibitor which previously had successfully been used to treat the cancer. The term "acquired resistance" indicates that the cancer becomes resistant to the effects of the drug after being exposed to it for a certain period of time. For example, gastrointestinal stromal tumors (GIST), a mesenchymal tumor of the intestinal tract, and chronic myelogenous leukemia (CML) are treated with imatinib (STI571 or Gleevac), a tyrosine kinase inhibitor that inhibits the kinase activity of BCR-ABL, ABL, KIT, and PDGFR. It has shown been shown that, while patients may benefit from the treatment initially, many patients subsequently develop resistance to the agent. In some cases, this acquired resistance has been shown to result from a secondary

mutation in the gene associated with the cancer. For example, most GIST patients have an activating mutation in either the KIT or PDGFRA gene. A study of GIST patients with acquired resistance to imatinib showed secondary mutations in the KIT kinase domain. See, e.g., Antonescu et al, Clin. Cancer Res., 11(11):41824190, 2005. A second site mutation in BCR-ABL is the predominant mechanism of imatinib resistance in CML. See, e.g., Gorre et al., Science, 293:876-880, 2001 who describe a mutation T315I associated with imatinib resistance. Acquired resistance has also been observed with other cancer drugs, including patients treated with EGFR-kinase inhibitors, such as gefitinib (Iressa) or erlotinib (Tarceva). See, e.g., Kobayshi et al., N. Engl. J. Med., 352:786-792, 2005. Pao et al. (PLoS Med., 2, e73, 2005) observed that patients with progressing lung tumors contained, in addition to a primary drug-sensitive mutation in EGFR, a secondary mutation in the kinase domain which led to drug-resistance.

[0009] Resistance mutations often occur in the kinase catalytic domain interfering or weakening the interaction with its inhibitor. Resistance mutations have been reported for number of kinases, including, BCR-ABL, KIT, PGF receptor, and EGF receptor. These secondary mutations often occur in the "gatekeeper" residue, the amino acid residue that "guards" the ATP-binding pocket and which also can comprise the site which interacts with the inhibitor. See, e.g., Noble et al., Science, 303: 1800-1805, 2004.

[0010] Nonetheless, the present invention relates to using sorafenib to treat a cancer which has acquired resistance to a kinase inhibitor, irrespective of the molecular mechanism responsible for it.

[0011] Examples of mutations which can lead to resistance and which can be treated in accordance with the presence invention include, e.g., KIT mutations, such as primary or secondary mutations in residues 654, 670, 816, 820, 822, 823, from residues about 650-654, about 670-674, from about 816-824, in the A-loop (activation), V654A, T670I, D816G, D816E, D820E, D820Y, N822K, and Y823D, etc. Such mutations, when secondary, can include any primary mutation, especially mutations in Exon 11, such as V559D, etc. Examples of mutations which lead to gefitinib and erlotinib resistance,

include, e.g., mutations at residue 670, such as T790M (see also, Carter et al., Proc. Natl. Acad. Sci., 102:11011-11016, 2005).

[0012] Examples of kinase targets to which resistance can be acquired, included, but are not limited to, e.g., PDGFR-alpha, PDGFR-beta, EGFR, VEGFR, VEGFR1, VEGFR2, VEGFR3, HER-2, KIT, FLT3, c-MET, FGFR, FGFR1, FGFR3, c-FMS, RET, ABL, ALK, ARG, NTRK1m NTRK3, JAK2, ROS, etc. Associated cancers include, but are not limited to, CML (chronic myeloid leukemia), ALL (acute lymphoblastic leukemia), AML (acute myelogenous leukemia), T-ALL (T-Cell acute lymphoblastic leukemia), ALCL (acute lymphoblast cell leukemia), EMS (8p11 myeloproliferative syndrome), aCML (atypical chronic myelogenous leukemia), MM (multiple myeloma), T-lymphoma, MDS (myelodysplastic (syndrome), HES (hypereosinophilic syndrome), SM (systemic mastocytosis), and CMML (chronic myelomonocytic leukemia), IMT (inflammatory myofibroblastic tumor), NSCLC (non-small cell lung cancer), glioblastoma, SCCHN (squamous cell carcinoma of the head and neck), ovarian cancer, RCC (renal cell carcinoma), pancreatic cancer, colorectal cancer, breast cancer, lung cancer, GIST, seminoa, sarcomas, musculoskeletal tumors, gastric cancer, renal papillary carcinoma, malignant melanoma, PTC (papillary thyroid cancer), congenital fibrosarcoma, mesoblastic nephroma, secretory breast carcinoma, osteosarcoma, PAIS (pulmonary artery intimal sarcoma), DFSP (dermatofibrosarcoma protuberans), FMTC (familial medullary thyroid carcinoma), MEN-2B, radiation associated papillary thyroid cancer, astrocytoma, breast cancer, prostate cancer, renal cancer, etc. See, e.g., Krause et al., N. Engl. J., Med., 353:172-187, 2005. See, also any of the cancers listed in Table 1.

[0013] Diseases which can be treated in accordance with present invention include, e.g., diseases which are treated with imatinib, such as, but not limited to: Accelerated Phase Chronic Myelogenous Leukemia; Acute Erythroid Leukemia; Acute Lymphoblastic Leukemia; Acute Lymphoblastic Leukemia in Remission; Acute Lymphocytic Leukemia; Acute Monoblastic and Acute; Monocytic Leukemia; Acute Myelogenous Leukemia; Acute Myeloid Leukemia; Adenocarcinoma of the Prostate; Adenoid Cystic Carcinoma of the Head and Neck; Advanced Gastrointestinal Stromal Tumor; Agnogenic Myeloid; Metaplasia; Anaplastic Oligodendroglioma; Astrocytoma; B-Cell Adult Acute Lymphoblastic Leukemia; Blastic Phase Chronic Myelogenous

Leukemia; Bone Metastases; Brain Tumor; Breast Cancer; Cancer; Central Nervous System Cancer; Childhood Acute Lymphoblastic Leukemia; Childhood Acute Lymphoblastic Leukemia in Remission; Childhood Central Nervous System Germ Cell Tumor; Childhood Chronic Myelogenous Leukemia; Childhood Soft Tissue Sarcoma; Chordoma; Chronic Eosinophilic Leukemia (CEL); Chronic Idiopathic Myelofibrosis; Chronic Myelogenous Leukemia; Chronic Myeloid Leukemia; Chronic Myelomonocytic Leukemia; Chronic Phase Chronic Myelogenous Leukemia; Colon Cancer; Colorectal Cancer; Dermatofibrosarcoma; Dermatofibrosarcoma Protuberans (DFSP); Desmoid Tumor; Eosinophilia; Epidemic Kaposi's Sarcoma; Essential Thrombocythemia; Ewing's Family of Tumors; Extensive Stage Small Cell Lung Cancer; Fallopian Tube Cancer; Familiar Hypereosinophilia; Fibrosarcoma; Gastric Adenocarcinoma; Gastrointestinal Neoplasm; Gastrointestinal Stromal Tumor; Glioblastoma; Glioma; Gliosarcoma; Grade I Meningioma; Grade II Meningioma; Grade III Meningioma; Hematopoietic and Lymphoid Cancer; High-Grade Childhood Cerebral Astrocytoma; Hypereosinophilic Syndrome; Idiopathic Pulmonary Fibrosis; L1 Adult Acute Lymphoblastic Leukemia; L2 Adult Acute Lymphoblastic Leukemia; Leukemia, Lymphocytic, Acute L2; Leukemia, Myeloid, Chronic; Leukemia, Myeloid, Chronic Phase; Liver Dysfunction and Neoplasm; Lung Disease; Lymphoid Blastic Phase of Chronic Myeloid Leukemia; Male Breast Cancer; Malignant Fibrous Histiocytoma; Mastocytosis; Meningeal Hemangiopericytoma; Meningioma; Meningioma; Meningioma; Metastatic Cancer; Metastatic Solid Tumors; Myelofibrosis; Myeloid Leukemia, Chronic; Myeloid Leukemia, Chronic Accelerated-Phase; Myeloid Leukemia, Chronic, Chronic-Phase; Myeloid Metaplasia; Myeloproliferative Disorder (MPD) with Eosinophilia; Neuroblastoma; Non-T, Non-B Childhood Acute Lymphoblastic Leukemia; Oligodendroglioma; Osteosarcoma; Ovarian Germ Cell Tumor; Ovarian Low Malignant Potential Tumor; Ovarian Neoplasms; Pancreatic Cancer; Pelvic Neoplasms; Peritoneal Cavity Cancer; Peritoneal Neoplasms; Philadelphia Chromosome Positive Chronic Myelogenous Leukemia; Philadelphia Positive Acute Lymphoblastic Leukemia; Philadelphia Positive Chronic Myeloid Leukemia in Myeloid Blast Crisis; Polycythemia Vera; Pulmonary Fibrosis; Recurrent Adult Brain Tumor; Recurrent Adult Soft Tissue Sarcoma; Recurrent Breast Cancer; Recurrent Colon Cancer; Recurrent Esophageal Cancer; Recurrent

Gastric Cancer; Recurrent Glioblastoma Multiforme (GBM); Recurrent Kaposi's Sarcoma; Recurrent Melanoma; Recurrent Merkel Cell Carcinoma; Recurrent Ovarian Epithelial Cancer; Recurrent Pancreatic Cancer; Recurrent Prostate Cancer; Recurrent Rectal Cancer; Recurrent Salivary Gland Cancer; Recurrent Small Cell Lung Cancer; Recurrent Tumors of the Ewing's Family; Recurrent Uterine Sarcoma; Relapsing Chronic Myelogenous Leukemia; Rheumatoid Arthritis; Salivary Gland Adenoid Cystic Carcinoma; Sarcoma; Small Cell Lung Cancer; Stage II Melanoma; Stage II Merkel Cell Carcinoma; Stage III Adult Soft Tissue Sarcoma; Stage III Esophageal Cancer; Stage III Merkel Cell Carcinoma; Stage III Ovarian Epithelial Cancer; Stage III Pancreatic Cancer; Stage III Salivary Gland Cancer; Stage IIIB Breast Cancer; Stage IIIC Breast Cancer; Stage IV Adult Soft Tissue Sarcoma; Stage IV Breast Cancer; Stage IV Colon Cancer; Stage IV Esophageal Cancer; Stage IV Gastric Cancer; Stage IV Melanoma; Stage IV Ovarian Epithelial Cancer; Stage IV Prostate Cancer; Stage IV Rectal Cancer; Stage IV Salivary Gland Cancer; Stage IVA Pancreatic Cancer; Stage IVB Pancreatic Cancer; Systemic Mastocytosis; T-Cell Childhood Acute Lymphoblastic Leukemia; Testicular Cancer; Thyroid Cancer; Unresectable or Metastatic Malignant Gastrointestinal Stromal Tumor (GIST); Unspecified Adult Solid Tumor; Untreated Childhood Brain Stem Glioma; Uterine Carcinosarcoma, and Uterine Sarcoma.

[0014] Diseases which can be treated in accordance with present invention include, e.g., diseases which are treated with gefitinib, such as, but not limited to: Adenocarcinoma of the Colon; Adenocarcinoma of the Esophagus; Adenocarcinoma of the Lung; Adenocarcinoma of the Prostate; Adenocarcinoma of the Rectum; Advanced Adult Primary Liver Cancer; Advanced Non-Nasopharyngeal Head and Neck Carcinoma; Anaplastic Astrocytoma; Anaplastic Oligodendroglima; Anaplastic Thyroid Cancer; Bladder Cancer; Brain Tumor; Breast Cancer; Breast Cancer in Situ; Breast Neoplasms; Bronchoalveolar Cell Lung Cancer; Cancer of the Fallopian Tube; Carcinoma, Squamous Cell; Cervix Neoplasms; Colon Cancer; Colorectal Cancer; Epithelial Mesothelioma; Esophageal Cancer; Esophagogastric Cancer; Follicular Thyroid Cancer; Gastric Cancer; Gastrinoma; Gastrointestinal Carcinoid; Giant Cell Glioblastoma; Glioblastoma; Glioblastoma Multiforme; Head and Neck Cancer; Hepatocellular Carcinoma; Hypopharyngeal Cancer; Inoperable Locally Advanced

Squamous Cell Carcinoma of Head and Neck; Insulinoma; Intraductal Breast Carcinoma; Islet Cell Carcinoma; Large Cell Lung Cancer; Laryngeal Cancer; Lip and Oral Cavity Cancer; Lip Cancer; Liver Cancer; Lung Adenocarcinoma With Bronchiolo-Alveolar Feature; Lung Cancer; Male Breast Cancer; Medullary Thyrod Cancer; Meningeal Tumors; Metastatic Colorectal Cancer; Metastatic Gastrointestinal Carcinoid Tumor; Metastatic Pancreatic Carcinoma; Mixed Gliomas; Myelogenous Leukemia, Acute; Nasopharyngeal Carcinoma; Neuroblastoma; Non-Metastatic (T2-T4, N0-N3, M0; Stages II and III) and Histologically-Confirmed Intestinal GC; Non-Metastatic Prostate Cancer; Nonresectable Adrenocortical Carcinoma; Non-Small Cell Lung Cancer; Nose Cancer; Oligodendroglial Tumors; Oral Cancer; Oropharyngeal Cancer; Osteosarcoma; Ovarian Cancer; Ovarian Neoplasms; Pancreatic Cancer; Papillary Thyroid Cancer; Peritoneal Carcinoma; Pharynx Cancer; Pneumonic-Type Adenocarcinoma (P-ADC); Primary Hepatocellular Carcinoma; Prostate Cancer; Rectal Cancer; Recurrent Adult Primary Liver Cancer; Recurrent Breast Cancer; Recurrent Colon Cancer; Recurrent Endometrial Cancer; Recurrent Esophageal Cancer; Recurrent Glioblastoma; Recurrent Rectal Cancer; Recurrent Skin Cancer; Refractory Germ Cell Tumors Expressing EGRF; Renal Cell Cancer; Rhabdomyosarcomas; Sarcomatous Mesothelioma; Skin Cancer; Soft Tissue Sarcoma; Squamous Cell Carcinoma of the Esophagus; Squamous Cell Carcinoma of the Head and Neck; Squamous Cell Carcinoma of the Skin; Squamous Cell Lung Cancer; Stage II Esophageal Cancer; Stage III Esophageal Cancer; Synovial Sarcoma; Thorax and Respiratory Cancer; Throat Cancer; Thyroid Cancer; Transitional Cell Cancer of the Renal Pelvis and Ureter; Transitional Cell Carcinoma of the Bladder; Tubal Carcinoma; Unspecified Childhood Solid Tumor; Untreated Childhood Brain Stem Glioma; Urethral Cancer.

[0015] Diseases which can be treated in accordance with present invention include, e.g., diseases which are treated with tarceva, such as, but not limited to: Adenocarcinoma; Adenocarcinoma of the Colon; Adenocarcinoma of the Esophagus; Adenocarcinoma of the Lung; Adenocarcinoma of the Pancreas; Adenocarcinoma of the Prostate; Adenocarcinoma of the Stomach; Adenosquamous Cell Lung Cancer; Adult Giant Cell Glioblastoma; Advanced Adult Primary Liver Cancer; Advanced NSCLC;

Advanced Solid Tumors; Anaplastic Astrocytoma; Anaplastic Olligodendroglioma; Andrigen Deprivation Therapy; Bladder Cancer; Brenner Tumor; Bronchoalveolar Cell Lung Cancer; Childhood Brain Tumor; Childhood Cerebellar Astrocytoma; Childhood Cerebral Astrocytoma; Childhood Ependymoma; Childhood Malignant; Germ Cell Tumor; Childhood Oligodendroglioma; Colorectal Cancer; ECOG; Endometrial Adenocarcinoma; Endometrial Adenosquamous Cell; Esophageal Cancer; Extrahepatic Bile Duct Cancer; Fallopian Tube Cancer; Fallopian Tube Cancer; Female Reproductive Cancer; Gallbladder Cancer; Gastric Cancer; Gastrointestinal Cancer; Glioblastoma Multiforme; Gliosarcoma; Head and Neck Cancer; Head and Neck Neoplasms; High-Grade Childhood; Cerebral Astrocytoma; Hormone Sensitive Metastatic Breast Cancer; Hypopharyngeal Cancer; Kidney and Urinary Cancer; Laryngeal Cancer; Localized Unresectable Adult Primary liver Cancer; Low-Grade Childhood Cerebral Astrocytoma; Lung Adenocarcinoma With Bronchiolo-Alveolar Feature; Male Breast Cancer; Meningioma; Mesothelioma; Mixed Gliomas; Nasopharyngeal Cancer; Neoplasms; Neurofibrosarcoma; Non-Metastatic Prostate Cancer; Non-Small-Cell Lung; Oral Cavity Cancer; Oropharyngeal Cancer; Ovarian Cancer; Ovarian Epithelial Cancer; Ovarian Neoplasms; Pancreatic Cancer; Peritoneal Cavity Cancer; Pharynx Cancer; Pharynx Neoplasms; Pneumonic-Type Adenocarcinoma (P-ADC); Primary Hepatocellular Carcinoma; Primary Liver Cancer; Prostate Cancer; Prostate Cancer, Androgen Independent; Pulmonary Diseases; Recurrent Adult Brain Tumor; Recurrent Adult Primary Liver Cancer; Recurrent Breast Cancer; Recurrent Cervical Cancer; Recurrent Endometrial Cancer; Recurrent Esophageal Cancer; Recurrent Pancreatic Cancer ; Recurrent Renal Cell Cancer; Relapsed/Refractory Non-Small-Cell Lung Cancer; Renal Cell Carcinoma; Rising Prostate Specific Antigen (PSA); Soft Tissue Sarcoma; Squamous Cell Carcinoma; Squamous Cell Carcinoma of the Esophagus; Squamous Cell Carcinoma of the Lip and Oral Cavity; Squamous Cell Carcinoma of the Oropharynx; Stage II Pancreatic Cancer; Stage III Pancreatic Cancer; Stage IIIA Non-Small Cell Lung Cancer; Stage IIIB or IV Non-Small Cell Lung Cancer; Stage IV Breast Cancer; Stage IV Colon Cancer; Stage IV Endometrial Cancer; Stage IV Rectal Cancer; Thorax and Respiratory Cancer; Transitional Cell Carcinoma of the Bladder; Tumors

Metastatic to Brain; Unspecified Adult Solid Tumor; Upper Aerodigestive Tract Neoplasms.

[0016] Examples of tyrosine kinase inhibitors and other kinase inhibitors, include, but are not limited to, e.g., ABX-EGF, adaphostin, AEE788, AG 013736, AG 490, AG 825, AG 957, AG 1024, AG 1296, aloisine, aloisine A, alsterpaullone, aminogenistein, AMG 706, AMN107, API-2, AP23573, apigenin, ARRY-142886 (AZD6244), arctigenin, AY-22989, AZD0530, AZD1152, AZD2171, bevacizumab, bisindolylmaleimide IX, BMS-354825, BMS-387032, BMS-599626, Bryostatin 1, CCI779, CEP-701, CEP-7055, cetuximab, 2C4, chelerythrine, CHIR-258, CI-1033, CPT-11, CP724714, CGP52421, CP-547-632, CT52923, CYC202, D816X, DMPQ, DRB, erlotinib (tarceva or OSI774), edelfosine, erbstatin analog, ET18OCH3, everolimus (RAD0001), fasudil, FK506, gefitinib (ZD1839), GO 6976, GW2974, GW572016, GW786034, imatinib mesylate (STI57 or Gleevec), H-7, H-8, H-89, HA-100, HA-1004, HA-1077, HA-1100, hydroxyfasudil, Isis 3521, indirubin-3'-oxime, 5-Iodotubercidin, kenpaullone, KN-62, KY12420, lapatinib ditosylate (GSK572016), LFM-A13, limofosine, luteolin, LY294002, LY294002, LY333531, LY379196, mallotoxin, midostaurin, ML-9, MLN518, NSC-154020, NSC-226080, NSC-664704, NSC-680410, NU6102, olomoucine, oxindole I, PD 0173074, PD 0325901, PD 153035, PD 98059, PD 169316, PD 184352, phloridzin, Perifosine, PKC412, piceatannol, picropodophyllin, PP1, PP2, purvalanol A, PTK787 (ZK 2222584; vatalanib), quercetin, RAPA, rapamune, rapamycin, R0 318220, R0 320432, roscovitine, rottlerin, SB202190, SB203580, sirolimus, SL327, SMS-354825, SP600125, staurosporine, , STI-571, SU101, SU1498, SU4312, SU6656, SU5402, SU5416, SU6668, SU11248, sunitinib (sutent), syk inhibitor, TBB, TCN, Triciribine, Tyrphostin AG 490, Tyrphostin AG 825, Tyrphostin AG 957, Tyrphostin AG 1024, trastuzumab (herceptin), wortmannin, XL647, XL999, Y-27632, U0126, UCN-01, VX-680, ZD6474, ZM 252868, and analogs and derivatives thereof, etc.

[0017] Specific examples of tyrosine kinase inhibitors include, e.g., AEE788, AMG 706, AMN107, ARRY-142886 (AZD6244), AZD2171, AZD0530, bevacizumab, BMS-354825, BMS-599626, CCI779, CEP-7055, cetuximab, CHIR-258, CI-1033, CP-724714, CP-547-632, erlotinib (tarceva or OSI774), gefitinib (Iressa), GW572016, GW786034, imatinib mesylate (STI57 or Gleevec), lapatinib ditosylate (GSK572016), PD 0173074,

PD 0325901, PKC412, PTK787, rapamycin, sunitinib (sutent), SU5416, SU11248, SU6668, trastuzumab, XL647, ZD6474, and analogs and derivatives thereof.

[0018] Further examples of tyrosine kinase inhibitors, include, e.g., 17-DMAG; 17-AAG; AG 9; AG 10; AG 1; AG 18; AG 30; AG 43; AG 82; AG 99; AG 112; AG 126; AG 183; AG 213; AG 370: AG 490; AG 494; AG 527; AG 537; AG 538; AG 555; AG 556; AG 592; AG 825; AG 835; AG 879; AG 957; AG 957; AG 1024; AG 1288; AG 1295; AG 1296; AG 1387; AG 1433; AG 1478; AGL 2043; AGL 2263; Aminogenistein; BPDQ; BPIQ-I; BPIQ-II; 4-[(3'-Bromo-4'-hydroxyphenyl)amino]-6,7-dimethoxyquinazoline (WHI-P154); 4-[(3-Bromophenyl)amino]-6,7-diethoxyquinazoline; Butein; (5-Butanoate-1H-2-indolyl)(1H-2-indolyl)-methanone; 4-[(4'-Chloro-2'-fluoro)phenylamino]-6,7-dimethoxyquinazoline; N-(4-Chlorophenyl)-2-[(pyridin-4-ylmethyl)amino]benzamide; CL-387785; Cucurbitacin I, Cucumis sativus L.; Curcumin, Curcuma longa L.; Daidzein; Damnacanthal; Daphnetin; 5'-Deoxy-5'-methylthioadenosine; 4-(3',5'-Dibromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P97); (Z)-5-Bromo-3-(4,5,6,7-tetrahydro-1H-indol-2-ylmethylene)-1,3-dihydroindol-2-one; 2-(1,1-Dimethylethyl)-9-fluoro-3,6-dihydro-7H-benz[h]-imidaz[4,5-f]isoquinolin-7-one; 4-(6,7-Dimethoxy-4-quinazolinyl)-N-(4-phenoxyphenyl)-1-piperazinecarboxamide; 3-[(2,4-Dimethylpyrrol-5-yl)methylidene]-indolin-2-one (SU5416); (Z)-3-[(2,4-Dimethyl-3-(ethoxycarbonyl)pyrrol-5-yl)methylidenyl]indolin-2-one; DMBI; Emodin; Erbstatin Analog; Geldanamycin (Streptomyces hygroscopicus); Genistein; Genistin; GTP-14564;

[0019] Other examples of tyrosine kinase inhibitors, include, but are not limited to, Herbimycin A (Streptomyces sp.); 1,2,3,4,5,6-Hexabromocyclohexane; HNMPA-(AM)3; (5-Hydroxy-1H-2-indolyl)(1H-2-indolyl)-methanone; 4-(4'-Hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P131); IGF-1R Inhibitor, PPP; I-OMe-AG 538; (Z,E)-3-(Imidazol-4-ylmethylene)indolin-2-one; [2-(1H-2-Indolylcarbonyl)-1H-5-indolyl]butanoate; Indirubin Derivative E804; K-252a, Nocardiopsis sp.; Lavendustin A; Lavendustin B; LFM-A11; LFM-A12; LFM-A13; MAZ51; 3-(1-Methyl-1H-indol-3-yl-methylene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonamide; 2-Naphthyl-(N-isopropyl,N-benzyl)-b-aminoethylketone, HCl; 2-Naphthylvinyl Ketone; Oxindole I; PD 153035; PD 156273; PD 158780; PD 168393; PD 174265; Piceatannol; PP1 Analog; PP1 Analog II (1NM-PP1); PP2; PP3; Quercetin; Radicicol (Diheterospora chlamydosporia); RG-13022; 4-

(4'-Phenoxyanilino)-6,7-dimethoxyquinazoline; p60v-src 137-157 Inhibitor Peptide (VAPSDSIQAEEWYFGKITRRE); ST638; SU11652; SU1498; SU4984; SU5402; SU5614; SU6656; (-)-Terreic Acid, Synthetic; 2'-Thioadenosine; Tyrene CR4; 3-(3-Thienyl)-6-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine; ZM323881; ZM 39923; and ZM 449829.

[0020] As indicated above, the present invention provides methods of treating cancers which have acquired resistance to a kinase inhibitor comprising, e.g., comprising administering to a subject in need thereof an effective amount of sorafenib, wherein the cancer is treated.

[0021] The phrase "effective amount" indicates the amount of sorafenib which is effective to treat any symptom or aspect of the cancer. Effective amounts can be determined routinely. Further guidance on dosages and administration regimens is provided below.

[0022] The term "treating" is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving, etc., one or more of the symptoms associated with a cancer, including all cancers mentioned herein and in Table 1. Administering effective amounts of sorafenib can treat one or more aspects of the cancer disease, including, but not limited to, causing tumor regression; causing cell death; causing apoptosis; causing necrosis; inhibiting cell proliferation; inhibiting tumor growth; inhibiting tumor metastasis; inhibiting tumor migration; inhibiting tumor invasion; reducing disease progression; stabilizing the disease; reducing or inhibiting angiogenesis; prolonging patient survival; enhancing patient's quality of life; reducing adverse symptoms associated with cancer; and reducing the frequency, severity, intensity, and/or duration of any of the aforementioned aspects.

[0023] Any cancer can be treated in accordance of the present invention, irrespective of the type or cause of the cancer, and irrespective of the genetic lesions associated with it (see, e.g., Atlas of Genetics and Cytogenetics in Oncology and Haematology on the worldwide web at infobiogen.fr/services/chromcancer/ for an atlas of genes involved in cancer). In addition to treating cancer, pre-cancerous cells, tumors, neoplasms, and non-malignant tumors can also be treated.

[0024] Cancers which can be treated include, e.g., cancers which are primary; which arise from a primary tumor at a secondary metastatic site; which have been treated by surgery (e.g., entirely removed, surgical resection, etc); which have been treated by chemotherapy, radiation, radiofrequency ablation, and/or any other adjunct to drug therapy; which have acquired drug-resistance; which are refractory to a chemotherapeutic agent.

[0025] Any subject can be in accordance with the present invention, including, e.g., mammals, such as dogs, cats, horses, rats, mice, monkeys, and humans.

[0026] In addition to kinase inhibitors, the present invention also relates to treating a cancer which has acquired resistance to any agent targeted at the RAS-RAF-MEK-ERK pathway. Agents include any compound which is an inhibitor of any component of the aforementioned pathway.

[0027] The present invention also provides methods of treating a cancer in a subject in need thereof, comprising administering an effective amount of sorafenib to said subject having a cancer, wherein said cancer is refractory to a chemotherapeutic agent. The term "refractory" means, e.g., that the cancer (including a tumor and/or any metastasis thereof), upon treatment with at least one chemotherapeutic shows no or only weak anti-cancer (e.g., anti-proliferative response) (such as, no or only weak inhibition of tumor growth) after the treatment with such an agent. Thus, after a patient has been treated with a chemotherapeutic agent with success, but subsequent treatments show no or little affect, the cancer can be described as being refractory to the agent. Examples of chemotherapeutic agents include, but are not limited to, e.g., alkylating agents (e.g., cyclophosphamide, ifosfamide, melphalan, chlorambucil, aziridines, epoxides, alkyl sulfonates), cisplatin and its analogues (e.g., carboplatin, oxaliplatin), antimetabolitites (e.g., methotrexate, 5-fluorouracil, capecitabine, cytarabine, gemcitabine, fludarabine), toposiomerase interactive agents (e.g., camptothecin, irinotecan, topotecan, etoposide, teniposide, doxorubicin, daunorubicin), antimicrotubule agents (e.g., vinca alkaloids, such as vincristine, vinblastine, and vinorelbine; taxanes, such as paclitaxel and docetaxel), interferons, inteleukin-2, histone deacetylase inhibitors, monoclonal antibodies, estrogen modulators (e.g., tamoxifen, toremifene, raloxifene), megestrol, aromatase inhibitors (e.g., letrozole, anastrozole,

exemestane, octreotide), octreotide, anti-androgens (e.g., flutamide, casodex), etc. See, e.g. Cancer: Principles and Practice of Oncology, 7th Edtion, Devita et al, Lippincott Williams & Wilkins, 2005, Chapters 15, 16, 17, and 63.

[0028] The term "sorafenib" as used herein refers to the tosylate salt of the compound N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl} urea of the formula I below including all polymorphs, hydrates, solvates or combinations thereof.

[0029] The compound N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl} urea of formula I below and all polymorphs, hydrates, solvates or combinations thereof are also suitable for use in this invention.

[0030] In addition, pharmaceutically acceptable salts of the compound of formula I, other than sorafenib, are also suitable for use in this invention, as are their polymorphs, hydrates, solvates or combinations thereof. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2}, Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, N,N-diethylamine, N,N-dicyclohexylamine, lysine, pyridine, N,N-dimethylaminopyridine (DMAP), 1,4-diazabiclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

[0031] Solvates for the purposes of the invention are those forms of the compound where solvent molecules form a complex in the solid state and include, but are not limited to for example ethanol and methanol. Hydrates are a specific form of solvates, where the solvent molecule is water.

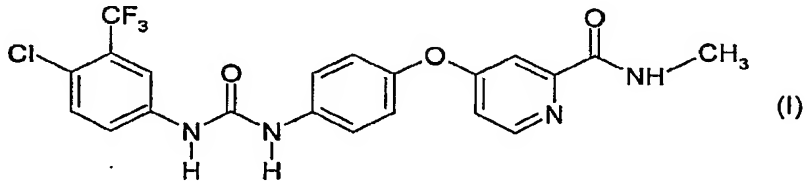
[0032] Without further elaboration, it is believed that one skilled in the art can, using the prceeding description, utilize the following invention to its fullest extent. The following specific preferred embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

[0033] In the forgoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and, all parts and percentages are by weight, unless otherwise indicated.

EXAMPLES

[0034] The invention will be explained below with reference to the following non-limiting examples.

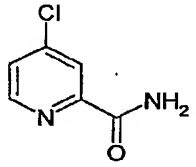
[0035] Formula I is as follows:



(I)

[0036] The compound N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl} urea can be prepared by the following multistep procedure:

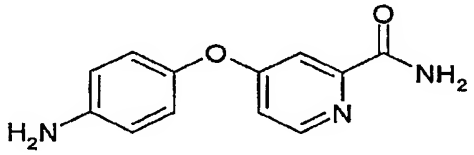
[0037] Step 1: Preparation of 4-chloro-2-pyridinecarboxamide



[0038] To a stirred mixture of methyl 4-chloro-2-pyridinecarboxylate hydrochloride (1.0 g, 4.81 mmol) dissolved in conc. aqueous ammonia (32 mL) is added ammonium chloride (96.2 mg, 1.8 mmol, 0.37 equiv.), and the heterogeneous reaction mixture is stirred at ambient temperature for 16h. The reaction mixture is poured into EtOAc (500 mL) and water (300 mL). The organic layer is washed with water (2 x 300 mL) and a

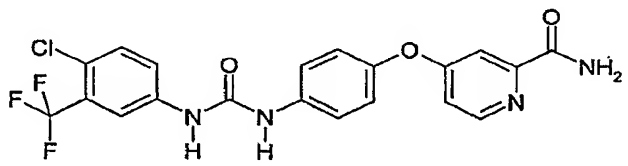
saturated NaCl solution (1 x 300 mL), dried ($MgSO_4$), concentrated in *vacuo* to give 4-chloro-2-pyridinecarboxamide as a beige solid (604.3 mg, 80.3%): TLC (50% EtOAc / hexane) R_f 0.20; ^{1}H-NMR (DMSO-d_6) □ 8.61 (d, J = 5.4 Hz, 1H), 8.20 (broad s, 1H), 8.02 (d, J = 1.8 Hz, 1H), 7.81 (broad s, 1H), 7.76 to 7.73 (m, 1H).

[0039] Step 2: Preparation of 4-(4-aminophenoxy)-2-pyridinecarboxamide



[0040] To 4-aminophenol (418 mg, 3.83 mmol) in anh DMF(7.7 mL) is added potassium *tert*-butoxide (447 mg, 3.98 mmol, 1.04 equiv.) in one portion. The reaction mixture is stirred at room temperature for 2 h, and a solution of 4-chloro-2-pyridinecarboxamide (600 mg, 3.83 mmol, 1.0 equiv.) in anh DMF (4 mL) is then added. The reaction mixture is stirred at 80 °C for 3 days and poured into a mixture of EtOAc and a saturated NaCl solution. The organic layer is sequentially washed with a saturated NH_4Cl solution then a saturated NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product is purified using MPLC chromatography (Biotage®; gradient from 100% EtOAc to followed by 10% MeOH / 50% EtOAc / 40% hexane) to give the 4-chloro-5-trifluoromethylaniline as a brown solid (510 mg, 58%). ^{1}H-NMR (DMSO-d_6) □ 8.43 (d, J = 5.7 Hz, 1H), 8.07 (br s, 1H), 7.66 (br s, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.07 (dd, J = 5.7 Hz, 2.7 Hz, 1H), 6.85 (d, J = 9.0 Hz, 2 H), 6.62 (d, J = 8.7 Hz, 2H), 5.17 (broad s, 2H); HPLC EI-MS *m/z* 230 ($(M+H)^+$.

[0041] Step 3: Preparation of N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea



[0042] A mixture of 4-chloro-5-trifluoromethylaniline (451 mg, 2.31 mmol, 1.1 equiv.) and 1,1'-carbonyl diimidazole (419 mg, 2.54 mmol, 1.2 equiv.) in anh dichloroethane (5.5

mL) is stirred under argon at 65 °C for 16 h. Once cooled to room temperature, a solution of 4-(4-aminophenoxy)-2-pyridinecarboxamide (480 mg, 2.09 mmol) in anh THF (4.0 mL) is added, and the reaction mixture is stirred at 60°C for 4 h. The reaction mixture is poured into EtOAc, and the organic layer is washed with water (2x) and a saturated NaCl solution (1x), dried ($MgSO_4$), filtered, and evaporated in *vacuo*. Purification using MPLC chromatography (Biotage®; gradient from 100% EtOAc to 2% MeOH / EtOAc) gave N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea as a white solid (770 mg, 82%): TLC (EtOAc) R_f 0.11, 100% ethyl acetate ^{1}H-NMR (DMSO-d_6) □ 9.21 (s, 1H), 8.99 (s, 1H), 8.50 (d, J = 5.6 Hz, 1H), 8.11 (s, 1H), 8.10 (s, 1H), 7.69 (broad s, 1H), 7.64 (dd, J = 8.2 Hz, 2.1 Hz, 1H), 7.61 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 2.5 Hz, 1H), 7.15 (d, J = 8.9 Hz, 2H), 7.14 (m, 1H); MS LC-MS (MH^+ = 451). Anal. calcd for $C_{20}H_{14}ClF_3N_4O_3$: C 53.29% H 3.13% N 12.43%. Found: C 53.33% H 3.21% N 12.60%.

[0043] Other methods of preparing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea are described in Bankston et al. "A Scaleable Synthesis of BAY 43-9006: A Potent Raf Kinase Inhibitor for the Treatment of Cancer" Org. Proc. Res. Dev. 2002, 6(6), 777-781, and WO 00/42012 and WO 00/41698.

[0044] An example of the preparation of sorafenib in the polymorph II is s follows:

[0045] 903 g of 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methylpyridine-2-carboxamide, prepared as described above, are initially charged in 2700 ml of ethanol. 451.7 g of p-toluenesulfonic acid monohydrate are dissolved in 1340 g of ethanol and added dropwise at room temperature. The suspension is stirred at room temperature for 1 hour, then filtered off with suction, and the residue is washed three times with 830 ml each time of ethanol. The drying is effected at 50°C under reduced pressure with supply of air. 1129.6 g of the title compound in the polymorph II are obtained.

[0046] An example of the preparation of sorafenib in the polymorph I is as follows:

[0047] Heating 5mg of "Sorafenib,"[tosylate salt of 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]-phenoxy}-N-methylpyridine-2-carboxamide] in the polymorph II to 200°C at a heating rate of 20°C/min and

subsequently cooling to room temperature at a cooling rate of 2°C/min. The sample is tested thermoanalytically (DSC) and corresponds to the title compound in the polymorph I.

[0048] The specific dose level and frequency of dosage may vary, depending upon a variety of factors, including the activity of the active agent, its metabolic stability and length of action, rate of excretion, mode and time of administration, the age, body weight, health condition, gender, diet, baseline hematologic and biologic parameters (e.g., WBCs, granulocytes, platelets, hemoglobin, creatinine, bilirubin, albumin, etc.), etc., of the subject, and the severity, intensity, stage of the cancer, primary site of cancer, size of cancer lesion, presence or extent of metastases, surgical status, disease progression (i.e., aggressive), etc. of the disease.

[0049] The compound of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intraperitoneal, topical, transdermal (e.g., using any standard patch), ophthalmic, nasally, local, non-oral, such as aerosal, spray, inhalation, subcutaneous, intravenous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, intrathecal, intratumoral, etc. Sorafenib can be administered directly to the site of a tumor, either pre- or post-operatively. It can be administered alone, or in combination with any ingredient(s), active or inactive.

[0050] Sorafenib can be administered by the oral route using the pharmaceutical composition of the present invention will generally range, based on body weight, from about 0.01 mg/kg to about 50 mg/kg; from about 1 mg/kg to about 40 mg/kg; from about 5 mg/kg to about 30 mg/kg; from about 10 to about 25 mg/kg; about 10 mg/kg; about 20 mg/kg; about 25 mg/kg; about 30 mg/kg; etc.

[0051] Any suitable dosing interval can be used in accordance with the present invention. For example, the compound can be administered once, twice (BID), three, four, etc., times a day. For example, about 100, about 200, about 400 mg, about 500 mg, about 600 mg, or about 800 mg can be administered one, twice, or three times daily.

[0052] Sorafenib can be administered at any suitable time. For example, it can be administered routinely as other chemotherapeutic agents; it can be administered as a

bolus prior to a surgical intervention; prior to or after radiation, radiofrequency ablation and other energy treatments; post-operatively; pre-operatively; etc.

[0053] Sorafenib can be further combined with any other suitable additive or pharmaceutically acceptable carrier. Such additives include any of those used conventionally, such as those described in Remington: The Science and Practice of Pharmacy (Gennaro and Gennaro, eds, 20th edition, Lippincott Williams & Wilkins, 2000); Theory and Practice of Industrial Pharmacy (Lachman et al., eds., 3rd edition, Lippincott Williams & Wilkins, 1986); Encyclopedia of Pharmaceutical Technology (Swarbrick and Boylan, eds., 2nd edition, Marcel Dekker, 2002).

[0054] The compounds can be in any suitable form, without limitation. Forms suitable for oral use, include, but are not limited to, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, solutions, syrups and elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions.

[0055] Compounds can be formulated with other ingredients, e.g., "pharmaceutically acceptable carriers" or "excipients" to indicate they are combined with the active drug and can be administered safely to a subject for therapeutic purposes. These include, but are not limited to, antioxidants, preservatives, dyes, tablet-coating compositions, plasticizers, inert carriers, excipients, polymers, coating materials, osmotic barriers, devices and agents which slow or retard solubility, etc.

[0056] Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations.

[0057] Non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc.

[0058] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0059] Aqueous suspensions containing the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0060] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

[0061] The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set

forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0062] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0063] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[0064] The compounds may also be administered in the form of suppositories for rectal or vaginal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature or vaginal temperature and will therefore melt in the rectum or vagina to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0065] Compounds of the invention may also be administrated transdermally using methods known to those skilled in the art (see, for example: Chien; "Transdermal Controlled Systemic Medications"; Marcel Dekker, Inc.; 1987. Lipp et al. WO94/04157 3Mar94). For example, a solution or suspension of a compound of Formula I in a suitable volatile solvent optionally containing penetration enhancing agents can be combined with additional additives known to those skilled in the art, such as matrix materials and bacteriocides. After sterilization, the resulting mixture can be formulated following known procedures into dosage forms. In addition, on treatment with emulsifying agents and water, a solution or suspension of a compound of Formula I may be formulated into a lotion or salve.

[0066] Suitable solvents for processing transdermal delivery systems are known to those skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol, lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate, polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane or benzene, or halogenated hydrocarbons such as dichloromethane, chloroform, trichlorotrifluoroethane, or trichlorofluoroethane. Suitable solvents may also include mixtures of one or more materials selected from lower alcohols, lower ketones, lower carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

[0067] Suitable penetration enhancing materials for transdermal delivery system are known to those skilled in the art, and include, for example, monohydroxy or polyhydroxy alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated C8–C18 fatty alcohols such as lauryl alcohol or cetyl alcohol, saturated or unsaturated C8–C18 fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to 24 carbons such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tertbutyl or monoglycerin esters of acetic acid, capronic acid, lauric acid, myristinic acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate, diisopropyl sebacate, diisopropyl maleate, or diisopropyl fumarate. Additional penetration enhancing materials include phosphatidyl derivatives such as lecithin or cephalin, terpenes, amides, ketones, ureas and their derivatives, and ethers such as dimethyl isosorbid and diethyleneglycol monoethyl ether. Suitable penetration enhancing formulations may also include mixtures of one or more materials selected from monohydroxy or polyhydroxy alcohols, saturated or unsaturated C8–C18 fatty alcohols, saturated or unsaturated C8–C18 fatty acids, saturated or unsaturated fatty esters with up to 24 carbons, diesters of saturated or unsaturated discarboxylic acids with a total of up to 24 carbons, phosphatidyl derivatives, terpenes, amides, ketones, ureas and their derivatives, and ethers.

[0068] Suitable binding materials for transdermal delivery systems are known to those skilled in the art and include polyacrylates, silicones, polyurethanes, block polymers, styrenebutadiene copolymers, and natural and synthetic rubbers. Cellulose ethers, derivatized polyethylenes, and silicates may also be used as matrix

components. Additional additives, such as viscous resins or oils may be added to increase the viscosity of the matrix.

[0069] Compositions comprising precursors can also be formulated for controlled release, where release of the active ingredient is regulated or modulated to achieve a desired rate of delivery into the systemic circulation. A controlled release formulation can be pulsed, delayed, extended, slow, steady, immediate, rapid, fast, etc. It can comprise one or more release formulations, e.g. extended- and immediate- release components. Extended delivery systems can be utilized to achieve a dosing internal of once every 24 hours, once every 12 hours, once every 8 hours, once every 6 hours, etc. The dosage form/delivery system can be a tablet or a capsule suited for extended release, but a sustained release liquid or suspension can also be used. A controlled release pharmaceutical formulation can be produced which maintains the release of, and or peak blood plasma levels of sorafenib.

[0070] In preferred solid oral pharmaceutical compositions according to the invention, at least 80% of the sorafenib exists in the stable polymorph I form and most preferably sorafenib is present in a micronized form.

[0071] Micronization can be achieved by standard milling methods, preferably by air chat milling, known to a skilled person. The micronized form can have a mean particle size of from 0.5 to 10 µm, preferably from 1 to 6 µm, more preferably from 1 to 3 µm. The indicated particle size is the mean of the particle size distribution measured by laser diffraction known to a skilled person (measuring device: HELOS, Sympatec).

[0072] Pharmaceutical compositions which are preferred comprise sorafenib, a compound of formula (I) or another pharmaceutically acceptable salt of a compound of formula I in a portion of at least 40%, preferably at least 45%, more preferably at least 50%, even more preferably at least 55%, by weight of the composition. Amounts of at least 62%, or at least 69%, or at least 75% by weight of the composition can be used under certain circumstances. Methods for preparing such formulations are disclosed in provisional application Serial No. 60/658,827, filed March 7, 2005, which is incorporated herein by reference.

[0073] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The

preceding preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

[0074] In the foregoing and in the examples, all temperatures are set forth uncorrected in degrees Celsius and, all parts and percentages are by weight, unless otherwise indicated.

[0075] The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

[0076] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

[0077] It is believed that one skilled in the art, using the preceeding information and information available in the art, can utilize the present invention to its fullest extent. It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein. The topic headings set forth above and below are meant as guidance where certain information can be found in the application, but are not intended to be the only source in the application where information on such topic can be found. All publications and patents cited above are incorporated herein by reference.

What we claim:

1. A method of treating a cancer in a subject in need thereof, comprising:

administering an effective amount of sorafenib to said subject having a cancer, wherein said cancer has acquired resistance to a tyrosine kinase inhibitor.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/044238

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/435 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/009367 A (AMBIT BIOSCIENCES CORP [US]; BIGGS III WILLIAM H [US]; CARTER TODD [US) 3 February 2005 (2005-02-03) paragraphs [0006], [0011] - [0021.0042.] claims 17-20	1
X	WO 03/047523 A (ONYX PHARMA INC [US]) 12 June 2003 (2003-06-12) figures 3,4 page 4, lines 4-11 examples 1,2 claims 1-5,9	1

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 April 2007	20/04/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bazzanini, Rita

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/044238

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHOI YUN-JUNG ET AL: "IMATINIB-RESISTANT CELL LINES ARE SENSITIVE TO THE RAF INHIBITOR BAY 43-9006" BLOOD, W.B.SAUNDERS COMPANY, ORLANDO, FL, US, vol. 100, no. 11, 10 December 2002 (2002-12-10), page ABSTRACT1427, XP009080845 ISSN: 0006-4971 abstract	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/044238

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 1 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/044238

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005009367 A	03-02-2005	NONE	
WO 03047523 A	12-06-2003	AU 2002365899 A1	17-06-2003
		CA 2466762 A1	12-06-2003
		EP 1578346 A2	28-09-2005
		JP 2005526008 T	02-09-2005